Symmetric bilateral caudate, hippocampal, cerebellar, and subcortical white matter MRI abnormalities in an adult patient with heat stroke

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Heat stroke is the end result of excess heat stress and results in multiorgan dysfunction with a propensity for central nervous system (CNS) injury. Damage to the CNS appears to be the result of multiple mechanisms, including direct heat damage and the initiation of a sepsis-type syndrome. Only a few scattered case reports exist in the literature that document CNS damage via imaging. We present a case with symmetric bilateral magnetic resonance findings in the caudate nuclei, subcortical white matter, hippocampi, and cerebellum. To our knowledge, this is the first case to report symmetric bilateral caudate abnormality and bilateral hippocampal enhancement.

A 54-year-old African American man found unresponsive by emergency medical services presented to the emergency department at Baylor University Medical Center with hypotension, altered mental status, respiratory failure, and a temperature of 108°F. The patient had a recent history of severe burns to 50% of his body requiring skin grafting. The family reported that he had abused cocaine for the past 2 days since being discharged from an outside hospital for a skin graft infection.

Shortly after admission, the patient developed alteration in his hemostasis profile, which was felt to be secondary to development of disseminated intravascular coagulation (DIC). DIC was treated with fresh frozen plasma.

IMAGING FINDINGS

The initial computed tomography (CT) scan revealed diffuse cerebral edema *(Figure 1a)*. Follow-up CT performed 2 days after admission showed complete resolution of the cerebral edema *(Figure 1b)*. The patient continued to demonstrate altered mental status, and as a result magnetic resonance imaging (MRI) was performed.

Diffusion-weighted images from MRI 5 days after admission revealed symmetric diffusion hyperintensity within the bilateral cerebellar hemispheres, bilateral caudate heads, and hippocampi *(Figure 2)*. A definite corresponding decrease in apparent diffusion coefficient (ADC) was not noted. However, it is not known if an ADC decrease would have been present had MRI been performed at the time of initial insult. There was corresponding increased T2 and fluid-attenuated inversion recovery (FLAIR) signal at these locations, suggesting edema. Given the symmetric nature and the recent history of extreme hyperthermia/heat stroke, these findings were felt to be most compatible with neurologic sequelae of heat stroke.

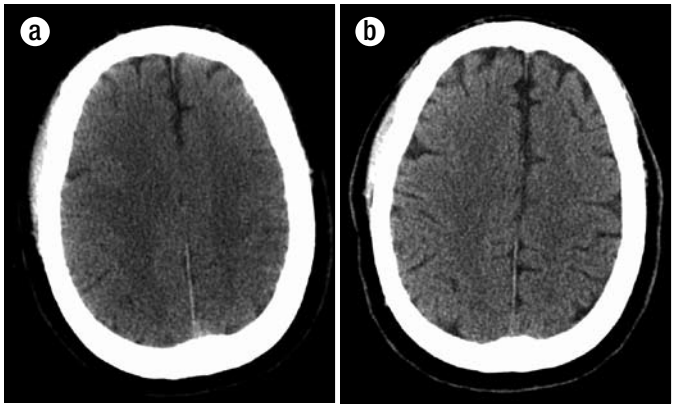

Figure 1. Initial head CT and short-term follow-up head CT. **(a)** CT from admission reveals diffuse edema with effacement of sulci near the vertex. **(b)** Follow-up CT 2 days after admission shows interval resolution of edema.

Follow-up MRI 9 days after the initial presentation revealed a few foci of T1 shortening and gradient recalled echo (GRE) blooming at the site of the previous bilateral cerebellar abnormality compatible with blood product. T2 and FLAIR signal abnormality within the hippocampi and cerebellar hemispheres showed improvement, with stable abnormality within the caudate bodies. New enhancement was identified at the site of the previous cerebellar and hippocampal abnormality. In addition, there was interval development of small subcortical foci of T2/FLAIR hyperintensity within the bilateral hemispheres *(Figure 3)*.

Follow-up CT 3 months after admission revealed small bilateral cerebellar foci of hypoattenuation compatible with encephalomalacia. No obvious abnormality was noted within the caudate nuclei or hippocampi.

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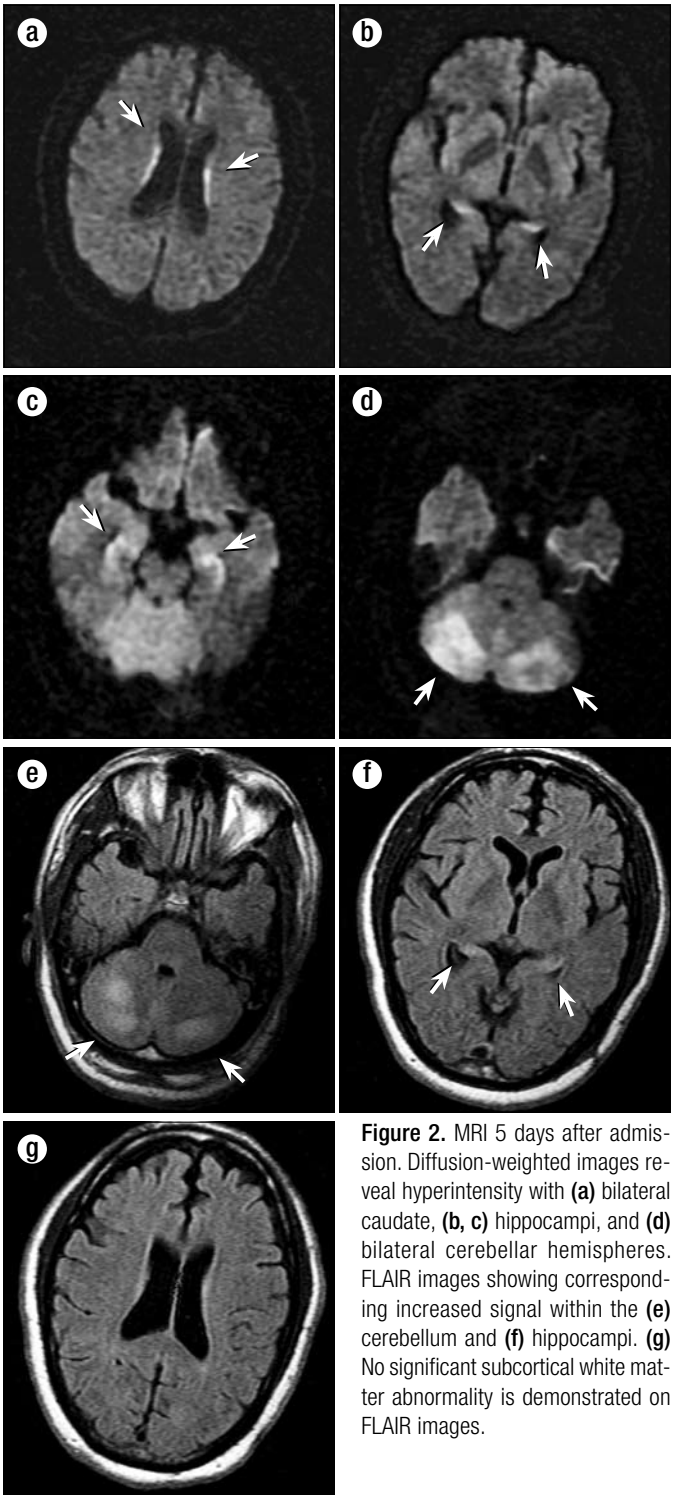

Figure 2. MRI 5 days after admission. Diffusion-weighted images reveal hyperintensity with **(a)** bilateral caudate, **(b, c)** hippocampi, and **(d)** bilateral cerebellar hemispheres. FLAIR images showing corresponding increased signal within the **(e)** cerebellum and **(f)** hippocampi. **(g)** No significant subcortical white matter abnormality is demonstrated on FLAIR images.

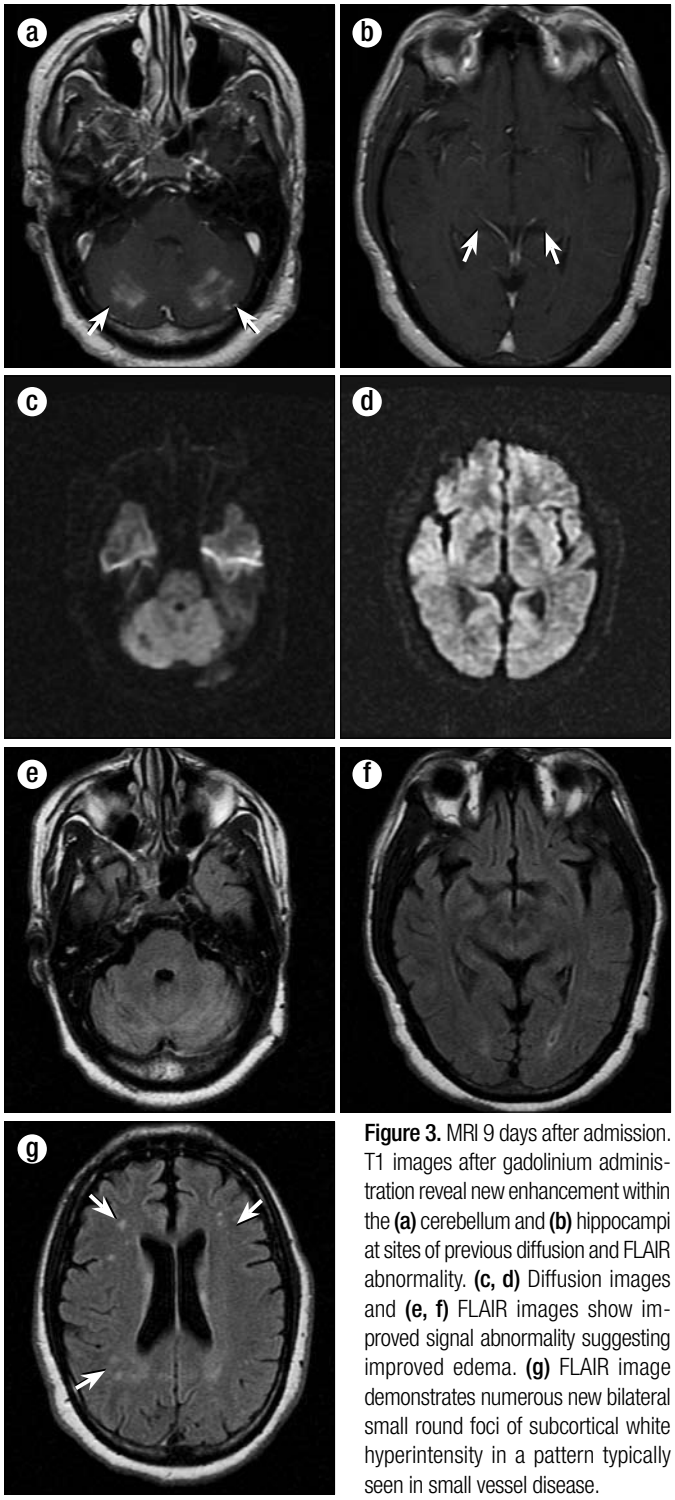

Figure 3. MRI 9 days after admission. T1 images after gadolinium administration reveal new enhancement within the **(a)** cerebellum and **(b)** hippocampi at sites of previous diffusion and FLAIR abnormality. **(c, d)** Diffusion images and **(e, f)** FLAIR images show improved signal abnormality suggesting improved edema. **(g)** FLAIR image demonstrates numerous new bilateral small round foci of subcortical white hyperintensity in a pattern typically seen in small vessel disease.

DISCUSSION

Heat stroke is the result of increased heat stress, due either to increased external exposure to heat or excess exertion. With heat stroke, thermoregulation fails, which results in core body temperature above 40°C and multiorgan dysfunction involving the central nervous system (CNS) in virtually all cases. If not treated early, many cases are fatal or result in irreversible brain damage. The importance of heat stroke as a cause of global mortality and morbidity will only increase with worsening global warming (1, 2).

More recent insight into the mechanism of heat stroke has revealed that the body's response to heat stress is complex. The most accepted model proposes a sepsis-like phenomenon. Normally in response to a heat stress, blood flow is directed to the periphery to help dissipate heat, which results in shunting of blood from the splanchnic vessels. There is also an increased acute-phase response with activation of the cytokine system (1). Finally, there is upregulation of heat shock protein synthesis (1, 3). As the heat load increases, the body becomes more volume and salt depleted. This results in splanchnic ischemia, which

increases bowel permeability. Gut bacteria produces endotoxin, which leaks into the bloodstream due to the increased gut permeability initiated by bowel ischemia. It is proposed that this endotoxin release results in an exaggerated inflammatory acute-phase response similar to sepsis. This exaggerated inflammatory response leads to a sepsis-like syndrome with multiorgan failure and alteration in hemostasis (1).

Damage by heat stroke to the CNS is proposed to occur by many mechanisms. One mechanism involves damage from the excess cytokines seen in heat stroke. Increased cytokines can result in increased leakiness of the blood-brain barrier or blood–cerebrospinal fluid (CSF) barrier. This results in brain vasogenic edema, which can be transient or eventually result in cell death (1). How vasogenic edema can cause permanent cell damage is not known. One theory is that prolonged edema results in decreased local cerebral blood flow, which when combined with global hypoperfusion from peripheral shunting of blood can result in ischemic cell death (1, 4). In addition to causing vasogenic edema, cytokines such as interleukin-1 recruit inflammatory cells or can induce apoptosis, both of which can also result in cell death (3, 5, 6). Animal models blocking the cytokine pathway have blunted damage from heat stroke, giving support to the sepsis-like inflammatory response as a mechanism for heat stroke (1, 3, 4).

There are also additional ways heat stress can result in CNS damage. In addition to the mechanism of ischemia discussed above, another means for ischemic change in heat stroke involves the altered hemostasis. Microvascular disease such as DIC that occurs with the sepsis-like syndrome seen in heat stroke can result in small vessel ischemic damage (1, 2).

Finally, heat itself can be directly toxic. For example, cerebellar Purkinje cells are known to be especially sensitive to direct heat (2, 3). Not surprisingly, cerebellar Purkinje cells have the highest concentration of heat shock protein in animal models of heat stress in order to help combat this increased sensitivity (3).

Though there has been much study and postulation on the mechanism of heat stroke, there is not much information on the typical location of brain injury from heat stroke. Postmortem studies dating back from 1916 to 1956 showed damage to the cerebellum, with additional findings in the cortex and brain stem (2, 7). Bazille in 2005 showed cerebellar atrophy as a common finding in a series of three postmortem patients (8). Previous radiologic studies have shown delayed cerebellar atrophy as a typical finding in line with this recent postmortem series. Many patients with heat stroke often present with cerebellar symptoms such as ataxia (2, 9, 10).

Diffuse cortical findings have also been described with heat stroke. A pediatric case report from 1996 of a child suffering from heat stroke revealed diffuse cerebral edema with eventual cortical laminar necrosis in the vascular boundary zones, suggesting an ischemic component to the mechanism of heat damage (11).

A few scattered case reports have revealed noncortical involvement with heat stroke. In 1995, Biary et al published a report of a patient with brain MRI performed 2 weeks after heat stroke. MRI revealed increased T2 signal within the left caudate and patchy increased T2 signal within the bilateral subcortical/periventricular white matter. MRI 6 months later revealed diffuse cerebellar atrophy (12).

A case report from 2003 of a patient with heat stroke revealed a bilateral external capsule, bilateral putamen, and a bilateral cerebellar process with probable blood products on T2- and T1-weighted images and some enhancement on gadolinium images. The authors suggested a small-vessel ischemic etiology for the findings, given that these findings are often seen in subacute infarction. They also proposed that the cerebellar findings were MRI precursors for delayed atrophy seen in past cases (13).

A publication in 2007 showed a case of bilateral hippocampi, patchy bilateral junctional zone, and bilateral cerebellar abnormalities on T2/FLAIR images in a pediatric case of heat stroke (14). Though findings vary in the few reported cases and postmortem studies, the cerebellum seems to be especially prone to heat-induced injury. This is somewhat expected given the known sensitivity of the Purkinje cells to direct heat damage.

Our case of heat stroke is interesting because it demonstrates a combination of findings that were reported separately in different case reports with the addition of never-reported findings. Transient diffuse cerebral edema that was present initially in our case has been reported in the past. The cerebellar findings on T2 and FLAIR sequences are also similar to findings in a few prior case studies. Cerebellar enhancement and blood product are similar to the prior case report from 2003. The case report from 1995 revealed isolated left-sided caudate T2 abnormality, but our case is the first to report bilateral symmetric caudate T2/FLAIR abnormality in heat stroke. White matter disease in our case is also similar to the case report from 1995. Our case is the second case report to reveal abnormality within the hippocampi, with the first being the case from 2007. It is the first to show enhancement within the hippocampi.

As described above, it appears that heat stroke can cause neurologic damage in a myriad of ways, all of which may have been involved in our case. Heat can cause direct toxicity, especially to heat-sensitive cells such as Purkinje cells. Through the stimulation of a sepsis-like syndrome, heat stress can induce breakdown of the blood-brain and blood-CSF barriers and result in vasogenic edema. Finally, some investigators propose that ischemic injury can be induced though a combination of microvascular coagulopathy and severe edema/hypoperfusion.

An interesting animal model by Sharma et al involves the administration of Evans blue to rats exposed to heat stress with poststress brain dissection to help elucidate regions of blood-CSF breakdown during heat stress. In their model, Evans blue had the greatest degree of increased staining relative to controls within the dorsal hippocampi, caudate nuclei, mid thalami, hypothalamus, and ventral cerebellum (15, 16). This finding suggests that these are the areas susceptible to increased blood-CSF breakdown after exposure to heat stress, and thus they may be more susceptible to damage by heat stroke. Case reports with findings of hippocampal, thalamic, and cerebellar findings give some credence to this mechanism for neurologic injury in heat

stroke. Findings within the caudate in the 1995 case and our case also support this mechanism. Similar breakdown of the blood-brain barrier may be the cause of diffuse cortical edema reported in the literature and also seen initially in our case.

Findings in our case are probably secondary to a mixture of the different mechanisms that have been proposed to cause CNS damage in heat stroke. Transient diffuse cerebral edema in our case could represent vasogenic edema from the blood-brain barrier breakdown. Diffusion hyperintensity and eventual enhancement within the cerebellum and hippocampi could be secondary to direct heat damage, vasculopathy with ischemic change, or blood-CSF barrier breakdown with resulting edema and possible ischemic change. Cytotoxic edema due to cell death was not definitively noted with our case. Cytotoxic edema usually demonstrates diffusion hyperintensity and decreased ADC on MRI. Both MRIs in our case did not definitively demonstrate decreased ADC, but this may have been a timing issue, as the initial MRI was performed 5 days after the initial insult. However, delayed subacute enhancement and blood product seen on the MRI 9 days after admission are findings that can be seen with cell death, secondary either to infarction or direct damage, and would support this mechanism of damage in our case. A future case of heat stroke with MRI imaging in the immediate acute phase would help shed further light on this issue. The findings in the caudate nuclei may represent vasogenic edema from blood-CSF barrier breakdown without definite cell death given lack of enhancement. Subcortical findings are in a pattern often seen in small vessel disease such as vasculitis and may be secondary to small vessel occlusion from our patient's DIC.

As is often the case with heat stroke, our unfortunate patient demonstrated severe neurologic damage and was aphasic at the time of discharge to a long-term care facility. A CT from 3 months after the heat stroke revealed bilateral cerebellar encephalomalacia in line with published data on findings in heat stroke. The patient's severe burns, preexisting skin infection, and cocaine abuse probably made him more vulnerable to heat stress and may have contributed to the development of heat stroke.

CONCLUSION

Past postmortem and imaging studies have revealed that the cerebellum is very sensitive to heat stress, and heat stroke should be included in the differential diagnosis of a patient with bilateral cerebellar findings. The most recent case reports all share in common cerebellar findings but differ in supratentorial findings, which vary between cases. Past reported findings include symmetric abnormality within the bilateral thalami, putamen, external capsules, and hippocampi. There has also been one case reporting unilateral caudate abnormality and bilateral subcortical white matter disease. Our case is interesting in that it demonstrates a combination of these reported findings including hippocampal, caudate, cerebellar, and subcortical white matter abnormality. To our knowledge, our case is the first to report symmetric bilateral caudate abnormality and symmetric hippocampal enhancement. Our patient also demonstrated transient diffuse cerebral edema, which has also been reported in cases of heat stroke.

In summary, when symmetric findings that suggest metabolic/toxic injury are encountered, scrutiny should be given to the specific location. If the findings localize to the cerebellum, heat stroke should be included in the differential diagnosis. Varying supratentorial findings have now been reported in the literature to include abnormality within the hippocampi, caudate nuclei, putamen, external capsules, thalami, or subcortical white matter.

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